

**REMARKS**

Reconsideration and withdrawal of the rejections set forth in the Office Action dated April 24, 2006 are respectfully requested.

**I. Amendments**

**A. Amendments to the Specification**

The application has been amended to remove a claim to the benefit of co-pending U.S. Application No. 09/910,406, filed July 19, 2001; to U.S. Provisional Application No. 60/219,128, filed July 19, 2000; and to Japanese Application No. 317160 filed October 17, 2000.

Typographical errors in paragraphs [0042] and [0082] are corrected.

**B. Amendments to the Claims**

Claims 1 and 8 are amended to recite that the method for increasing IL-10/IL-12 ratio in a multiple sclerosis patient involves administering IFN $\tau$  to obtain an increase in IL-10/IL-12 blood ratio, and continuing to administer to maintain the increased ratio. The claims are also amended to recite that the IFN $\tau$  protein has at least 80% sequence identity with SEQ ID NO:2. Basis for the 80% identity limitation is found in paragraph [0037].

Dependent claims are amended (claim 6) or canceled (claims 2, 5, 7, 9, and 12014) consistency with the changes to claims 1 and 8.

**II. Rejection Under 35 U.S.C. § 112, second paragraph**

Claims 1-7 were rejected under 35 U.S.C. §112, second paragraph as allegedly incomplete for omitting essential steps. Specifically, the Examiner noted a disconnect between the claim 1 preamble and the final step.

Both the preamble and final method step of claim 1 are amended as noted above to recite that the method for increasing IL-10/IL-12 ratio in a multiple sclerosis patient involves administering IFN $\tau$  to obtain an increase in IL-10/IL-12 blood ratio, and continuing to administer to maintain the increased ratio.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

### III. Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-14 were rejected under 35 U.S.C. §112, first paragraph as allegedly not enabling a skilled person to make and use the invention commensurate with the scope of the claims. The Examiner raised two matters: (1) that the breadth of the claims is excessive because they read on methods using any protein with 70% or greater homology to known IFN $\tau$  sequences and (2) that the breadth of the claims is excessive because they read on any autoimmune disorder.

Claims 1-14 were rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts that due to the breadth of IFN $\tau$  proteins within the claim scope, Applicants have not fully described the genus of IFN $\tau$  proteins capable of increasing blood IL-10/IL-12 ratios.

Claim 1 and 8 are amended to recite a method for treating persons suffering from multiple sclerosis and to limit the IFN $\tau$  protein to one having at least 90% sequence identity with SEQ ID NO:2. In view of these amendments, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

### IV. Rejection Under 35 U.S.C. § 103

Claims 1-14 were rejected under 35 U.S.C. §103 as allegedly obvious over Soos et al., WO 97/3607 [sic, WO 97/33607], "Soos") in view of van Boxel-Dezaire et al. (*Ann. Neurol.*, 46:695 (1999)) and further in view of Petererit et al. (*J. Neurol. Sci.*, 206:209 (2003)). This rejection is respectfully traversed for the following reason.

#### A. The Present Claims

The present claims relate to a method of increasing the IL-10/IL-12 blood ratio in patients suffering from multiple sclerosis (MS). MS is a non-contagious, lifelong chronic disease that causes symptoms such as weakness, muscle stiffness, poor coordination and balance, tingling, numbness, tremors, blurred vision, and slurred speech. An estimated 400,000 Americans have MS, according to the National Multiple Sclerosis Society (NMSS). Every week, about 200 people in the United States are diagnosed

with the disease ([http://www.fda.gov/fdac/features/2005/205\\_ms.html](http://www.fda.gov/fdac/features/2005/205_ms.html), visited on July 16, 2006).

Today, there are six<sup>1</sup> FDA-approved drugs to lessen the likelihood of MS attacks on the market. These drugs have limited effectiveness in treating MS and are inconvenient because they must be taken via injection ([http://www.fda.gov/fdac/features/2005/205\\_ms.html](http://www.fda.gov/fdac/features/2005/205_ms.html), visited on July 16, 2006). The currently-available drugs are also toxic and cause unwanted side effects (Id.). For example, the approved interferon-beta compounds (Avonex<sup>®</sup>, Betaseron<sup>®</sup>, Rebif<sup>®</sup>) cause flu-like symptoms and reactions at the injection site. Copaxone<sup>®</sup> gives short term reactions of flushing, chest pain, heart palpitations, anxiety, and shortness of breath (Id.).

Another problem associated with the current interferon-beta therapies for MS is the induction of neutralizing antibodies (Killestein, J. et al., *Current Opin. in Neurology*, 18:253 (2005)). Neutralizing antibodies to interferon-beta reduce interferon-beta bioavailability and therapeutic efficacy (Id.). Researchers are currently conducting studies to understand the effect of dose and frequency of dosing on neutralizing antibody formation to understand whether an optimal interferon-beta regimen (dose and dosing frequency) can be identified (Id.).

It is also reported in the literature that despite some beneficial effects of the currently available treatments, all the treatments are only partially effective in treating MS (Kappos, L. et al., *J. Neurol.*, 251[Suppl 5]:V57-V64 (2004)). Moreover, the efficacy of the treatments have been shown to be dependent on dose and dose frequency, suggesting that for treatment of MS, appropriate dose selection is critical (Id.).

The present inventors have found that oral administration of interferon-tau, a protein that is not found in humans, at a dose greater than about  $5 \times 10^8$  Units/day,

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<sup>1</sup>The five treatments are Avonex (interferon beta-1a, Biogen Idec, Inc.); Betaseron (interferon beta-1b, Berlex Laboratories, Inc.); Rebif, (interferon-beta 1a, Serono Inc.); Copaxone (glatimer acetate, Teva NeuroScience Inc.); Novatrone (mitoxantrone, Serono Inc.). A sixth compound, Tysabri (natalizumab, Biogen Idec, Inc.), was approved by the FDA but was voluntarily suspended from the market in Feb. 2005 due to two serious adverse events, including one death. However, tysabri has recently been re-approved by the FDA for marketing.

provides a beneficial increase in blood IL-10/IL-12 ratios, which leads to a beneficial clinical outcome, such as reduction in new brain lesions<sup>2</sup>.

**B. The Applied Art**

Soos describes oral administration of IFN $\tau$  for treatment of multiple sclerosis.

VAN BOXEL-DEZAIER disclose that multiple sclerosis is characterized by a decreased IL-10 level and increased IL-12 levels.

PETEREIT teach that multiple sclerosis patients with higher IL-10 levels correlates with higher disability score clinically.

**C. Analysis**

According to the M.P.E.P. § 2143, "to establish a *prima facie* case of obviousness, three basic criteria must be met." The second and third criteria are that "there must be a reasonable expectation of success" and "the prior art references (or references when combined) must teach or suggest all the claim limitations."

First, and with respect to the requirement that the prior art references must teach or suggest all claim limitations, Applicants submit that the teaching of Soos, van Boxel-Dezaire, and Petereit fail to satisfy this requirement. Specifically, the combined teachings nowhere show or suggest increasing the IL-10/IL-12 blood ratio in multiple sclerosis patients by oral administration of IFN $\tau$  at a dose of greater than about  $5 \times 10^8$  Units/day.

Neither van Boxel-Dezaire nor Petereit provide any guidance for a suitable dosage. Soos discloses a dose range of between about  $1 \times 10^5$  and  $1 \times 10^8$ , preferably between about  $1 \times 10^6$  and  $1 \times 10^7$  units/day" (page 20, lines 1-2). Applicants submit that disclosure of this dosage range does not render obvious the present claims for at least the following reasons.

The teaching in Soos does not guide one to the presently claimed dose of greater than about  $5 \times 10^8$  Units, which is beyond the uppermost value of the range

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<sup>2</sup> The Examiner is directed to Applicants co-pending Application Seriaon No. 10/842,701, now allowed, in which data from a recent clinical trial on MS patients were submitted by way of Declaration.

disclosed in Soos. For selection of a dose based on the range disclosed in Soos, one might look to the doses exemplified in the EAE mouse model studies (Examples 1, 3, 5:  $1 \times 10^5$  units; Example 2,  $3 \times 10^5$  units). The exemplified doses of  $1 \times 10^5$  units/day and  $3 \times 10^5$  units/day are three orders of magnitude below the claimed dose.

Alternatively, and as proposed by the Examiner, one might look to the teaching by Soos that IFN $\tau$  lacks the toxicity associated with other interferons, and therefore optimizing the dosage would not likely harm the patient. However, there is nothing in Soos that would guide one to increase the dosage to the claimed dose. The statement that IFN $\tau$  lacks toxicity relative to other interferons at most leads one to try the highest dose of  $1 \times 10^7$  units disclosed in Soos. It is clear from the disclosure of Soos on page 20, lines 1-9 that this highest disclosed dose of  $1 \times 10^7$  units was intended as a dose that is higher than the dose used for interferon-beta at which patient toxicity was observed. Soos contemplates no dose higher than this, as evidenced by the final sentence that reads (In view of the lower toxicity of IFN $\tau$ , these higher effective dosages could be administered without the associated toxic side-effects (emphasis added).")

Second, Applicants submit that the criterion for obviousness that there be an expectation of success has not been met. Data presented in Figs. 1A and 1D of the present application suggest that doses to humans in the range disclosed by Soos may not be effective to increase IL-10 blood levels. There is not any teaching in Soos from which a skilled practitioner would base an expectation that the presently claimed dosage would provide a favorable clinical outcome in human MS patients, as the doses exemplified in the mouse studies of Soos were three orders of magnitude lower.

Applicants were the first to demonstrate that interferon-tau, when administered orally to human at a dose of greater than about  $5 \times 10^8$  U/day, is effective in increasing IL-10/IL-12 blood ratios for treatment of MS in humans<sup>3</sup>. The teaching in Soos does not provide any expectation of this result at the claimed dose. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

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<sup>3</sup>See footnote 2 above.

V. Double-Patenting Rejections

Claims 1-14 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over certain claims of nine co-pending and co-owned applications. Each of the rejections is addressed below.

1. Rejections Over Application Serial No. 10/825,382, 10/825,457, 10/824,710, 11/040,706, and 10/884,741

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 of application serial no. 10/825,382.

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6 of application serial no. 10/825,457.

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-4, 16-17 of application serial no. 10/824,710.

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6 and 25 of application serial no. 11/040,706.

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-4, 8-10, and 19-22 of application serial no. 10/884,741.

A Terminal Disclaimer prepared in accordance with 37 C.F.R. §1.321(b) and (c) is enclosed. The signed Terminal Disclaimer obviates the obviousness-type double patenting rejections based on the 10/825,382, 10/825,457, 10/884,741, 10/824,710, and 11/040,706.

2. Rejections Over Application Serial Nos. 11/112,369, 10/991,653, 10/719,472, and 10/346,269

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 17, and 18 of application serial no. 11/112,369. Applicants respectfully traverse this rejection.

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 and 5-11 of application serial no. 10/991,653. Applicants respectfully traverse this rejection.

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-4 of application serial no. 10/719,472. Applicants respectfully traverse this rejection.

Claims 1-14 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-5 of application serial no. 10/346,269. Applicants respectfully traverse this rejection.

A. Legal Standard

In determining whether a non-statutory basis exists for a double patenting rejection, the first question to be asked is - does any claim in the application define merely an invention that is merely an obvious of an invention claimed in the patent?. M.P.E.P. § 804 II.B.1.

A double patenting rejection of the obviousness type is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. § 103 except that the patent principally underlying the double patenting rejection is not considered prior art. M.P.E.P. § 804 II.B.1.

B. The Instant Claims

Instant claim 1 relates to a method of increasing the IL-10/IL-12 ratio in a multiple sclerosis subject by orally administering interferon-tau at a daily dose of greater than about  $5 \times 10^8$  Units. Instant claim 8 relates to a method of inhibiting progression of

MS in a human subject suffering from MS by orally administering interferon-tau at a daily dose of greater than about  $5 \times 10^8$  Units.

**C1. Analysis: Rejection Over Application Serial No. 11/112,369**

Instant claims 1-14 were rejected as being an obvious variation of claims 1, 17, and 18 of application serial no. 11/112,369 ("the '369 application").

Claim 1 of the '369 application relate to a method comprising the steps of (i) identifying a human subject having an IL-10 deficiency and (ii) administering IFN $\tau$  in an amount effective to increase blood IL-10 levels.

The instant claims lack a step of "identifying a subject having an IL-10 deficiency." To arrive at the instant claims from the claims in the '369 application, one would need to omit this step. Applicants submit that such an omission is not an obvious variation of the '369 application, since exclusion of one of two method steps is not a minor, obvious variation. Accordingly, withdrawal of the obviousness-type double patenting rejection over the '369 application is respectfully requested.

**C2. Analysis: Rejection Over Application Serial No. 10/991,653**

Instant claims 1-14 were rejected as being an obvious variation of claims 1 and 5-11 of application serial no. 10/991,653 ("the '653 application"). Claim 1 of the '653 application relate too a method for promoting weight loss in a human by administering IFN $\tau$ .

Applicants submit that the instant methods for increasing the IL-10/IL-12 ratio in a multiple sclerosis subject and for inhibiting progression of MS in a human subject suffering from MS are not obvious variations to promoting weight loss in a human. Accordingly, withdrawal of the obviousness-type double patenting rejection over the '653 application is respectfully requested.

C3. Analysis: Rejection Over Application Serial No. 10/719,472

Instant claims 1-14 were rejected as being an obvious variation of claims 1-4 of application serial no. 10/719,472 ("the '472 application"). Applicants note that claims 1-6 of the '472 application are now allowed.

Claim 1 of the '472 application relates to a method for treating, for example, an autoimmune condition by orally administering IFN $\tau$  to increase blood levels of oligoadenylyate synthetase (OAS), as evidenced by monitoring blood OAS levels to ascertain if the OAS level is increased.

Applicants submit that the instant claims are not merely an obvious variation of the '472 claims. There is no requirement in instant claims that blood OAS levels be increased, as is there no requirement that the blood OAS levels be monitored. To arrive at the instant claims one would need to omit these features from the '472 claims, which is not merely an obvious variation. Accordingly, withdrawal of the obviousness-type double patenting rejection over the '472 application is respectfully requested.

C4. Analysis: Rejection Over Application Serial No. 10/346,269

Instant claims 1-14 were rejected as being an obvious variation of claims 1-5 of application serial no. 10/346,269 ("the '269 application"). Claim 1 of the '269 application relates to a method of administering IFN $\tau$  by orally administering the protein to patients in a fasted state, in order to increase blood OAS level.

Applicants submit that the instant claims are not merely an obvious variation of the '269 claims. There is no requirement in instant claims that the patient be in a fasted state, nor that blood OAS levels be increased. To arrive at the instant claims one would need to omit these features from the '269 claims, which is not merely an obvious variation. Accordingly, withdrawal of the obviousness-type double patenting rejection over the '269 application is respectfully requested.

VI. Conclusion

In view of the foregoing, the claims pending in the application comply with the requirements of 35 U.S.C. § 112 and patentably define over the applied art. A Notice of Allowance is, therefore, respectfully requested. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 838-4410.

Respectfully submitted,

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